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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/509,418	07/11/2000	DONALD J KOROPATNICK	PM 266291	3674

7590 11/01/2002

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EXAMINER	
EPPS, JANET L	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 11/01/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/509,418	Applicant(s) KOROPATNICK ET AL.	
	Examiner Janet L Epps-Ford, Ph.D.	Art Unit 1635	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5-9,11,13 and 14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5-9,11,13 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *12* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Double Patenting

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3. Claims 1, 3, 5-8 and 13-14 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6,087,489. In the instant case an obvious-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

In the instant case, claims 1-10 of US Patent 6,087,489, recite antisense oligonucleotides of 8 to 30 nucleotides in length comprising a sequence that is complementary to a nucleic acid molecule encoding human thymidylate synthase, wherein said oligonucleotide is complementary to the 3' untranslated region of said nucleic acid molecule and inhibits the expression of said human thymidylate synthase, or wherein said oligonucleotide inhibits cell proliferation. Additionally, claims 4-7 of US Patent 6,087,489 recite wherein said antisense oligonucleotides contain phosphorothioate modified intersugar linkages, 2'-O-methoxyethyl and 5-methylcytosine modifications. The antisense oligonucleotides of claims 1-10 differs from claims 1, 3, 5-8 and 13-14 of the instant application in that these claims are not limited to: a) deoxyoligonucleotides of 8 to 50 nucleotides in length, b) a sequence according to SEQ ID NO: 1 or 2, c) compositions comprising said antisense compounds in a pharmaceutically acceptable carrier, d) a combination product comprising antisense deoxyoligonucleotides in combination with an anticancer agent.

However, it is noted that the invention of US Patent 6,087,489 encompass both oligoribonucleotides and deoxyoligonucleotides and furthermore encompass antisense compounds from about 5 to about 50 nucleotides in length as a preferred embodiment (see col. 7, lines 1-5 and lines 12-14). Additionally, col. 15, lines 4-42, of US Patent 6,087, 489 supports compositions comprising the antisense compounds targeting thymidylate synthase including buffers, diluents and other additives for parenteral administration, and combination products thereof comprising an anticancer agent, wherein said anticancer agent is Tomudex (especially col. 15, line 34). Furthermore, the antisense compound according to SEQ ID NO: 1 and 2 recited in claim 3 of the instant application are species of the broad genus of antisense compounds

recited in claim 1 of the referenced US Patent, such that the antisense compounds recited in claim 3 of the instant application anticipate the genus of issued claim 1.

Claims 1, 3, 5-8 and 13-14 can not be considered patentably distinct over claims 1-10 of the issued US Patent when there are specifically disclosed embodiments in US Patent 6,087,489, which clearly indicate that claims 1, 3, 5-8, and 13-14 of the instant application are merely obvious variations of the invention of claims 1-10 of the referenced patent. Specifically, it would have been obvious to one of ordinary skill in the art at the time of filing to modify the antisense oligonucleotides of claims 1-10 by selecting specifically disclosed embodiments that support those claims, i.e. deoxyoligonucleotides that are 8 nucleotides or 50 nucleotides in length, wherein said deoxyoligonucleotides comprise a sequence according to SEQ ID NO: 1 or 2, compositions thereof and combination products, as disclosed in US 6,087,489. One having ordinary skill in the art would have been motivated to make these modifications since these embodiments are all disclosed as being obvious variations of the invention set forth in claims 1-10 of US Patent 6,087,489.

Response to Arguments

4. Claims 9 and 11 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for the reasons of record set forth in the Official Action mailed January 31, 2001.

Applicant's arguments filed 3-05-2002 have been fully considered but they are not persuasive. Applicants traverse the instant rejection on the grounds that (1) *in vivo* data is not required under 35 USC § 112, first paragraph; (2) a specification disclosure which contains a

teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as if in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

However, contrary to Applicant's arguments, objective evidence has been provided which raises significant reason to doubt the objective truth of Applicant's statements, particularly since Applicant's specification is not commensurate in scope with the claimed invention. Applicant's claims read on treating cancer comprising administering to a human an effective amount of antisense deoxyoligonucleotide targeting thymidylate synthase alone or in combination with an anticancer agent, however Applicant's specification provides only *in vitro* examples wherein it is demonstrated how to use the compounds and compositions of the claimed invention. However, Applicant's specification fails to provide an adequate correlation between their *in vitro* data and predicting the behavior of the compounds of the present invention in a human. As set forth in the Office Action mailed 1-31-2001, there are a significant number of factors well known in the art, which contribute to the unpredictability associated with antisense therapy, of which Applicants have completely disregarded and have not provided any arguments that would indicate how the specification as filed provides sufficient guidance that would render these factors of no consequence to the practice of the present invention. See also, *In Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 52 USPQ2d 1129 (Fed. Cir. 1999), wherein the court held that claims in two patents directed to genetic antisense technology (which aims to

control gene expression in a particular organism), were invalid because the breadth of enablement was not commensurate in scope with the claims.

As stated previously, numerous factors complicate nucleic acid based therapy, which have not been overcome by routine experimentation. These include, the controlling the fate of the nucleic acid itself once administered to an individual (volume of distribution, rate of clearance into the tissues, etc.), controlling the *in vivo* consequences of altered gene expression and protein function, the fraction of nucleic acid taken up by the target cell population, predicting the trafficking of the genetic material within cellular organelles, the rate of degradation of the nucleic acid, and the stability of the nucleic acid within a cell. Therefore, based upon these considerations, it is concluded "extrapolations from in vitro uptake studies to predictions about *in vivo* pharmacokinetic behavior are entirely inappropriate".

Furthermore, even assuming that an effective TS antisense oligonucleotide is constructed, it is not evident that enough cells can be transfected to provide any therapeutic benefit, Applicants provided any guidance and/or instruction in this regard.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L Epps-Ford, Ph.D. whose telephone number is 703-308-8883. The examiner can normally be reached on M-T, Thurs-Friday 9:00AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703)-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-746-5143 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Janet L Epps-Ford, Ph.D.
Examiner
Art Unit 1635

JLE
October 30, 2002

SEAN McGARRY
PRIMARY EXAMINER
1635